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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,111	09/16/2003	Dolores Schendel	559412000200	6128

25226 7590 09/04/2007

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
09/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,111	SCHENDEL ET AL	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *23-30 and 32-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *23-30, 32-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 27 and 41 have been amended. Claims 23-30 and 32-46 are pending and under consideration.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-30 and 32-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 23-26 and 33, -42 and 34-46 are method claims reliant on the identity of proteins or peptides which are "derived from" autologous dendritic cells. Claims 27-30, 32 and 43 are drawn to pharmaceutical compositions comprising antigen-presenting cells into which proteins and/or peptides "derived from" tumors cells from a patient have been introduced. The specification fails to provide a definition for "derived from" which would limit the proteins and/or peptides to those which are obtained from autologous tumor cells without modification. Thus, when given the broadest reasonable interpretation, proteins and/or peptides derived from autologous tumor cells include modified proteins or peptides having structural alterations. The specification describes only proteins or peptides obtained from tumor cells without modification. Thus, the specification fails to adequately describe proteins or peptides which are "derived from" tumor cells and thus comprise structural alterations. One of skill n the art would reasonable conclude that applicant was not in possession of the claimed genus of derivatized proteins or peptides obtained from tumor cells.

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to

DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

In the instant case a statement that the proteins or peptides are "derived from" autologous tumor cells does not distinguish the genus of derived proteins from other genuses except by the process of derivation, and does not define the structural properties of the derivatives in terms of either structure or function.

Because the specification fails to adequately describe the genus of derivatized peptides or proteins on which the instant method claims depend, said methods are also not adequately described.

Amendment of claims 23 and 33 to specific that the peptides are obtained from autologous tumor cells, or isolated from autologous tumor cells will overcome the instant rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23, 27, 28, 30, 32, 33, 34, 37-40 and 43-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Ohno (U.S.Appn 2002/0168351).

Ohno disclose a method for treating cancer comprising the administration of chimeric cells comprising tumor cells fused to autologous dendritic cells [023, , 025]. Ohno discloses that the cancers which can be treated are cancer is selected from the group consisting of renal cell carcinoma, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemias, acute lymphocytic leukemia, acute myelocytic leukemia; chronic leukemia, polycythemia vera, lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease [0036], which fulfill the specific embodiments of claim 28, 34, 43 and 44. Ohno discloses that CTL in the patient receiving the fusions cells are stimulated by the presentation of mucin antigens or Her-2/neu epitopes [130] which fulfills the specific embodiments of claims 45 and 46. Ohno discloses intravenous, subcutaneous and intramuscular routes of administration of the fusion cells [0145] which fulfills the specific

embodiment of claim 37. Ohno meets the limitations of claims requiring RNA from tumor cells which has been introduced in recombinant form because the expression of the tumor cell peptides by the fused dendritic cell is a recombinant form of expression of the tumor cell RNA encoding the peptides. because the tumor cell peptides are now being expressed by the dendritic cell due to the fusion of the two cell types, and thus the limitation of "recombinant" is met. further, it would be inherent in the fusion cells of Ohno that proteins or peptides which are over expressed in the tumor cells would be expressed by the dendritic cell fusion via the over expressed RNA present in the tumor cell of the fusion.

Claims 23, 25, 27, 28, 30, 32, 33, 34, 36-40 and 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohno (U.S.Appn 2002/0168351) in view of Nair et al (WO 97/41210, cited in a previous Office action).

Ohno teaches fusions of autologous dendritic cells with tumor cells for the expression of the tumor cell peptides by the dendritic cell. Ohno does not teach autologous dendritic cells which are transfected with nucleic acids encoding tumor cell peptides to produce the expression of said peptides by the autologous dendritic cells.

Nair et al teach method for the loading of dendritic cells by introduction of a tumor associated RNA which is unfractionated or cDNA made by PCR (page 3, lines 13-19). Nair et al disclose that the method offers advantages in that there is no need to identify specific tumor rejection antigens and an immune response to unfractionated RNA or cDNA made therefrom elicits immune responses to several tumor antigens reducing the likelihood of escape mutants and extends the use of active immunotherapy to the treatment of cancers for which specific tumor antigens have not yet been identified which is the vast majority of cancers (page 9, lines 21-35). Nair et al teach a method for treating cancer comprising directly administering the loaded dendritic cells to a patient suffering from cancer (claims 51-53).

It would have been prima facie obvious at the time the claimed invention was made to substitute the RNA or cDNA transfected dendritic cells to a patient having cancer. One of skill in the art would have been motivated to do so by the teachings of Nair et l regarding the improvements associated with using unfractionated RNA for the loading of dendritic cells, and the administration the loaded dendritic cells as part of the immunotherapy as taught by Nair et al.

Claims 23-25, 27, 28, 30, 32, 33, 34, 36-46 rejected under 35 U.S.C. 103(a) as being unpatentable over Ohno (U.S.Appn 2002/0168351) and Nair et al (WO 97/41210) as applied to claims 23, 25, 27, 28, 30, 32, 33, 34, 36-40 and 43-46 above, and further in view of Storkus et al (U.S. 6,077,519, cited in a previous Office action).

Claims 24 and 41 embody the method of claim 23 wherein proteins, peptide, RNA, DNA or cDNA from several different tumor cell lines are introduced into the HLA-haploidentical APC. Claim 42 embodies the method of claim 41 wherein pooled cDNA from two or three different tumor cell lines is introduced.

The combination of Ohno and Nair et al render obvious the instant invention regarding the loading of haploidentical APC with unfractionated RNA or cDNA made therefrom from tumor tissue from the patient. The combination does not teach or suggest the use of multiple tumor cell lines as a source of peptides, RNA or cDNA for loading or pulsing dendritic cells.

Storkus et al teach that dendritic cells can be pulsed with HLA-attached allogeneic tumor cell lines as an alternative to acid eluted peptides from the patients tumor cells (column 12, lines 21-32). Storkus et al teach the administration of pulsed dendritic cells by intravenous routes (column 35, lines 53-60). Storkus et al teach that the invention be applied to treat colon, squamous, gastric, breast, prostate, lung, cervical and ovarian carcinomas. It is noted that prostate carcinomas would inherently express prostate specific membrane antigen.

It would have been prima facie obvious at the time the claimed invention was made to use pooled tumor cell acid eluted peptides or RNA or cDNA for pulsing or loading the dendritic cells used in the methods rendered obvious by the combination of Greenman et al and Nair et al. One of skill in the art would have been motivated to do so by the suggestion of Storkus et al that cell lines can be used as a source of tumor specific antigen peptides. One of skill in the art would have been motivated to look to this source in the event that no tumor material from the patient was available or insufficient. One of skill in the art would have been motivated to used pooled acid eluted peptides or unfractionated RNA or unfractionated cDNA from several different tumor cell lines because of the teachings of Nair et al regard tumor escape mechanisms. One of skill in the art would understand that providing a multitude of antigens to the dendritic

cell would compensate for the ability of a tumor to down regulate an antigen and escape immune surveillance. The more tumor specific antigens which can be expressed by the activated dendritic cells, the more populations of activated T cells will be available for recognition of tumor cells. Further, because the method is taught by Storkus et al to extend to the treatment of prostate cancer, the unfractionated RNA, cDNA made therefrom would inherently include prostate specific membrane antigen, PSMA, thus fulfilling the limitations of claims 45 and 46.

Claims 23, 27, 28, 30, 32, 33, 34, 37-40 and 43-46 rejected under 35 U.S.C. 103(a) as being unpatentable over Ohno (U.S.Appn 2002/0168351).

Claims 26 and 35 embody the methods of claim 23 and 33 respectively, wherein antigen-presenting cells of two different haploidentical individuals are used.

Ohno teaches using antigen-presenting cells which are autologous. Ohno does not teach dendritic cells from haploidentical individuals.

It would have been prima facie obvious to use a mixture of haploidentical dendritic cells and autologous dendritic cells in the event that there was a deficiency in the quantity of dendritic cells obtained from the patient. One of skill in the art would have been motivated to provide more dendritic cells in place of the autologous dendritic cells in order to obtain enough of the dendritic cell-tumor cell chimeric cells with which to treat the patient.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicants arguments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A. Canella/
Ph.D., Primary Examiner,
Art Unit 1643